SECTION C
Organic Chemistry

Organic Fluorine Compounds. Part XLI.[1] The Reaction of Hydrofluoric Acid with Cycloalkene Epoxides

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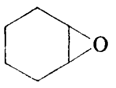
Aliphatic and simple cycloalkene epoxides fail to undergo transformation into fluorohydrins on treatment with hydrofluoric acid. A certain rigidity of the carbocyclic system is necessary for the reaction to be successful. Electron-withdrawing groups inhibit the ring-opening reactions even in rigid systems.

ALTHOUGH the preparation of fluorohydrins by the reaction of epoxides with anhydrous hydrofluoric acid is a reaction well known in the steroid series,[2] attempts to use the same method with aliphatic epoxides (1,2-epoxybutane, epichlorohydrin, ethyl 9,10-epoxystearate, and 2-cyano-2,3-epoxybutane) failed completely, nor could we substantiate the claim of Knunyants [3] that aliphatic epoxides can be transformed into fluorohydrins by the use of hydrofluoric acid in ether. Jullien *et al.*,[4] on the other hand, have successfully used amine hydrofluorides to open the heterocyclic ring in aliphatic and simple cycloaliphatic epoxides.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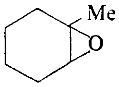
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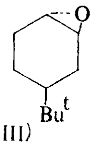
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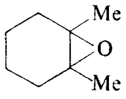
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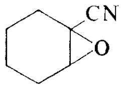
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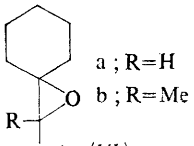

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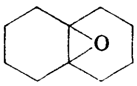
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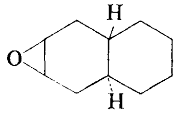
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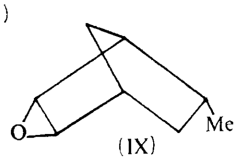
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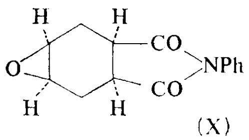
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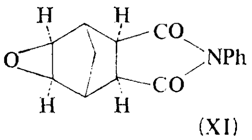
(XI)

If this difference in behaviour towards hydrofluoric acid is due to the rigidity of the steroidal ring system, it would be both theoretically interesting and of practical importance, to define the structure that can make a ring system sufficiently rigid to permit the opening of the epoxy-ring fused to it by hydrofluoric acid. Epoxycyclohexane (I) and 1,2-epoxy-1-methylcyclohexane (II) behaved exactly as the aliphatic compounds and gave no fluorohydrins. When, however, 4-t-butyl-1,2-epoxycyclohexane (III) reacted with hydrogen fluoride, a mixture of stereoisomeric fluorohydrins was obtained in 50% yield. Obviously, the bulky t-butyl group occupies the equatorial position and makes the compound rigid. This has been shown, by other means, by Winstein and Holness.[5] The same reasoning appears to apply—somewhat surprisingly—to 1,2-epoxy-1,2-dimethylcyclohexane (IV) which gave a mixture of fluorohydrins in 65% yield.

Electron-withdrawing groups as such do not enhance the ring opening in non-rigid systems. 1-Cyano-1,2-epoxycyclohexane (V), exactly as (II), gave no fluorohydrin, whilst the rigid 1-oxaspiro[2,5]octane-2-carbonitrile (VIa) afforded a fluorohydrin in 30% yield. It has been known that the analogous 2-methyl-1-oxaspiro-[2,5]octane-2-carbonitrile (VIb) reacts with hydrogen fluoride to give the corresponding fluorohydrin.[6] Indeed, Dreiding models show that (VIa) is more rigid than (II) in the part of the molecule involved in the reaction.

Confirmation of these results was obtained by examination of some bicyclic and tricyclic systems. The rigid 9,10-epoxydecalin (VII) gave a mixture of the epimeric fluorohydrins in a yield of 80%, and the somewhat less rigid 2,3-epoxydecalin (VIII) in a yield of 50%. The analogous fluorohydrin from 2,3-epoxy-1,2,3,4-tetrahydronaphthalene has been prepared by Arande *et al.*[4a] Similarly, 1,2-epoxy-3,6-endomethylene-4-methylcyclohexane (IX) gave the fluorohydrin in 49% yield. Electon-withdrawing groups in a rigid system appear to prevent the ring opening with hydrofluoric acid. Thus, neither 4,5β-epoxy-*N*-phenyl-*cis*-hexahydrophthalimide

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[4] (*a*) J. Jullien, J.-A. Martin, and R. Ramanadin, *Bull. Soc. chim. France*, 1964, 171; (*b*) G. Aranda, J. Jullien, and J.-A. Martin, *ibid.*, 1965, 1890; 1966, 2850.

[5] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

[6] G. Stork, W. S. Worrall, and J. J. Pappas, *J. Amer. Chem. Soc.*, 1960, **82**, 4315.

(X) nor the even more rigid *endo*-3,6-endomethylene-4,5β-epoxy-*N*-phenyl-*cis*-hexahydrophthalimide (XI) gave a fluorohydrin when treated with hydrogen fluoride.

It can thus be predicted that epoxides fused to a rigid system will give fluorohydrins with hydrogen fluoride, if no electron-withdrawing groups are present.

EXPERIMENTAL

The general method used was based on that of Henbest, Smith, and Thomas [2a] and will be illustrated for 9,10-epoxydecalin (VIII).

In a polyethylene vessel, a solution of (VIII) (33 g.) in a mixture of dry chloroform (50 ml.) and dry tetrahydrofuran (60 ml.) was cooled to 0°, and a cold solution of anhydrous hydrogen fluoride (42 g.) in dry chloroform (200 ml.) was added in small portions, with stirring, during 90 min. The solution (which turned red) was stirred at 0° for a further 90 min. and was then poured into an excess of aqueous potassium carbonate. The organic phase was separated, washed with water, and dried, and the solvent was removed through a short Vigreux column. The residue was distilled under reduced pressure and the fraction with b.p. 72—100°/0·2 mm. was redistilled, giving a mixture of two isomeric fluorohydrins (b.p. 75°/0·2 mm.). The mixture could be separated by v.p.c. into two compounds in the proportion of 1 : 3, but since the fluorohydrins are unstable unless kept over dry potassium fluoride at 0° and begin to decompose after 1—3 days, no preparative separation was attempted.

RESULTS

1,2-*Epoxy*-1,2-*dimethylcyclohexane* (IV).—This compound is reported in the literature,[7] but the yields were very small. It was, therefore, prepared by epoxidation of 1,2-dimethylcyclohexene (34 g.) according to the method of Danneel;[8] yield 23·5 g., b.p. 68°/30 mm. (Found: C, 76·0; H, 11·2. Calc. for $C_8H_{14}O$: C, 76·2; H, 11·1%.) The reaction of (IV) (18 g.) with hydrogen fluoride gave 2-fluoro-1,2-dimethylcyclohexanol (12·5 g.), b.p. 75°—95°/30 mm. and, on redistillation, b.p. 78—80°/30 mm. (Found: C, 65·4; H, 10·3; F, 12·5. Calc. for $C_8H_{15}FO$: C, 65·8; H, 10·3; F, 13·0%.)

4-*t*-*Butyl*-1,2-*epoxycyclohexane* (III).—This was prepared by the method of Sicher *et al.*[9] Compound (III) gave a fluorohydrin fraction (3·3 g.), b.p. 130—140°/30 mm. This fluorohydrin mixture is particularly unstable and decomposes completely within 24 hr. (Found: F, 10·6. $C_{10}H_{19}FO$ requires F, 10·9%).

1-*Oxaspiro*[2,5]*octane*-2-*carbonitrile* (VIa).—This was prepared by the method of Stork *et al.*[6] With hydrogen fluoride (9·5 g.) compound (VIa) (25 g.) gave a fluorohydrin fraction, b.p. 80—110°/2 mm., and on redistillation, 87—89°/2 mm. (Found: C, 63·0; H, 8·2; F, 10·8. Calc. for $C_8H_{12}FNO$: C, 61·1; H, 7·6; F, 12·1%).

9,10-*Epoxydecalin* (VII).—This was prepared by the method of Danneel.[8] The fairly unstable mixture of 9-fluoro-10-decalols had b.p. 75°/0·2 mm. (Found: C, 70·3; H, 9·9; F, 11·9. Calc. for $C_{10}H_{17}FO$: C, 69·8; H, 9·9; F, 11·1%)

2,3-*Epoxydecalin* (VIII).—This was prepared by the method of Henbest.[2a] With hydrogen fluoride compound (VIII) (10 g.) gave, in addition to much polymer, a fraction of b.p. 100—180°/0·5 mm. (5·5 g.) with, after repeated distillation, b.p. 115—118°/0·5 mm. The product was a mixture of 2-fluoro-3-decalols (Found: C, 70·1; H, 9·9; F, 10·3. $C_{10}H_{17}FO$ requires C, 69·8; H, 9·9; F, 11·1%).

1,2-*Epoxy*-3,6-endo*methylene*-4-*methylcyclohexane* (IX).—This was prepared from the known [10] bicyclo[2,2,1]-5-heptene-2-carbaldehyde as follows. From the aldehyde in two volumes of methanol and an equivalent of semicarbazide hydrochloride and sodium acetate dissolved in the minimum amount of water, the semicarbazone was prepared. It was filtered off, washed with cold water and a little ether, and air-dried, m.p. 164° (lit.,[11] 165°); yield 72%. The semicarbazone was used without purification in the next step. A mixture of the semicarbazone (47 g.), diethyleneglycol (250 ml.), hydrazine hydrate (98%) (25 g.), and potassium hydroxide was slowly heated to 190—200° and kept at this temperature for 2·5 hr.; the distillate which formed was collected. The mixture was then cooled to 110°, water (60 ml.) was added, and the mixture distilled again until the temperature reached 190°. Both distillates were combined, extracted with methylene chloride, washed with dilute hydrochloric acid and water, dried, and distilled. The oil (16 g.), b.p. 113°/700 mm. (lit.,[12] 115—117°/750 mm.) so obtained was epoxidized by the method of Danneel [8] during 9 hr. The *epoxide* (IX) was obtained in 68% yield, b.p. 75°/30 mm. (Found: C, 77·5; H, 9·6. $C_8H_{12}O$ requires C, 77·4; H, 9·7%). Compound (IX) gave, on reaction with hydrogen fluoride a fluorohydrin fraction (7 g.) b.p. 110—120°/30 mm. The *product* was rather unstable (Found: C, 66·3; H, 8·9; F, 12·9. $C_8H_{13}FO$ requires C, 66·7; H, 9·0; F, 13·2%).

4,5β-*Epoxy*-N-*phenyl*-cis-*hexahydrophthalimide* (X).—This was prepared from the known [13] *N*-phenyl-Δ^4-tetrahydrophthalimide by the method of Gray,[14] except that the time of the reaction was 5 hr. at 0—10°. From 27·3 g. of starting material 17 g. of crude product, m.p. 190—210°, was obtained. After two recrystallizations from chloroform–light petroleum (40—60°) the compound (5 g.) melted at 150° (Found: C, 69·4; H, 5·3. $C_{14}H_{13}NO_3$ requires C, 69·1; H, 5·3%).

On reaction with hydrogen fluoride, no fluorine-containing product could be isolated, and starting material was recovered.

endo-3,6-*Methylene*-4,5-*epoxy*-N-*phenyl*-cis-*hexahydrophthalimide* (XI).—This was similarly prepared from the known Δ^4-3,6-endomethylene-*N*-phenyltetrahydrophthalimide.[15] From (XI) (18 g.) the pure *epoxide* (5 g.), m.p. 200°, was obtained, after repeated recrystallizations from benzene (Found: C, 70·2; H, 4·9. $C_{15}H_{13}NO_3$ requires C, 70·6; H, 5·1%).

After treatment with hydrofluoric acid most of the material was recovered unchanged.

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Negative Experiments.—(a) 2,3-*Epoxybutane*. This was recovered unchanged to the extent of 61%, and 7% was isomerised to ethyl methyl ketone (identified by v.p.c.). The polymeric, nondistillable residue amounted to 25%.

(b) *Epichlorohydrin*. This was recovered in 85% yield on distillation. No carbonyl compounds and no polymers were formed.

(c) 2-*Cyano*-2,3-*epoxybutane*. This was recovered in 74% yield. V.p.c. of the product indicated the presence of 3-cyano-2-butanone and ethyl methyl ketone.

(d) *Epoxycyclohexane*. This gave, upon distillation of the reaction product, polymeric material (60%), cyclohexanone (19%) (identified by v.p.c.) and unchanged starting material (10%).

(e) 1,2-*Epoxy*-1-*methylcyclohexane*. Only 2% of the epoxy-compound was recovered, 10% was polymerised, and 55% was transformed into 2-methylcyclohexanone (v.p.c.).

(f) 1-*Cyano*-1,2-*epoxycyclohexane* was polymerised to the extent of 20% and rearranged to 2-cyanocyclohexanone (v.p.c.) to the extent of 63%. No unchanged starting material could be recovered.

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